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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/713,632	11/13/2003	Lawrence M. Kauvar	388512011000	2417

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EXAMINER	
SHAW, AMANDA MARIE	
ART UNIT	**PAPER NUMBER**
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/713,632	KAUVAR ET AL.	
	Examiner	Art Unit	
	Amanda M. Shaw	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 May 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 14, 2007 has been entered.

Claims 1-17 are currently pending and will be addressed herein. Claims 1 and 8 have been amended.

Withdrawn Rejections

2. The new matter rejection in section 2 of the Office Action of February 2, 2007 is withdrawn in view of amendments made to the claims.

The rejections made under 35 USC 112 2nd paragraph in section 3 of the Office Action of February 2, 2007 are withdrawn in view of amendments made to the claims.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

THE FOLLOWING IS A NEW GROUND OF REJECTION:

Claims 1-5, and 7-17 are rejected under 35 U.S.C. 102(b) as being anticipated by Bawendi et al (US Patent 6306610 Issued 10/2001).

Regarding Claim 1 Bawendi et al teaches a method wherein two oligonucleotide probes are hybridized to a target DNA sequences in close proximity. The two oligonucleotide probes are labeled with two differently colored nanocrystals that can be detected by a microscope (Column 5, lines 40-45 and Fig 3). In the instant case the nanocrystals taught by Bawendi et al are being interpreted as particulate labels because the fluorescent nanocrystals being used are known as Quantum Dots and are particulate and are labels, i.e., they have a diameter of between about 1 nm and about 1000nm (Column 6, lines 14-37). Bawendi specifically teaches that the method of the present invention is useful to determine the proximity of two or more biological compounds to each other and conversely can be used to determine that two or more biological compounds are not in proximity to each other (Column 24 lines 33-40). As illustrated in Fig 3. the paired probes having the first and second particulate labels hybridize to the target to provide the particulate labels as points separated by space. This separation in space is observed as a quenching effect whereby the presence of the pair identifies the desired region. Bawendi further exemplifies different ways of detecting the fluorescent nanocrystals, one of which uses a microscope (Column 27, lines 50-59). Thus Bawendi et al teach a method of contacting a sample with first and second probes which bracket a region and observing by microscopy the presence or

absence of any pairs of the first and second particulate labels as separate points in space.

Regarding Claims 2 and 3 Bawendi teaches that the two oligonucleotide probes are labeled with two differently colored nanocrystals, thus Bawendi teaches that the first and second particulate labels have first and second fluorophores that are distinguishable from each other (Column 5, lines 40-45 and Fig 3). Each nanocrystals is being interpreted as a different fluorophore because each one has different fluorescent properties.

Regarding Claim 4 Bawendi teaches that the nucleic acid probes of the invention are composed any type of polynucleotide including DNA, RNA, and PNA (Column 7 line 26 – Column 8 line 29).

Regarding Claim 5 Bawendi teaches that the first and second probes are complementary to sequences upstream and downstream sequences bracketing the region (Fig 3).

Regarding Claim 7 Bawendi discloses a multiplexed method using semiconductor nanocrystals having distinct emission spectra which can be used to detect simultaneously in the range of 2 to 10,000 analytes (Column 11, lines 44-54). Thus Bawendi teaches a method that can be performed simultaneously on a multiplicity of targets using a multiplicity of probes having particulate labels of different hues wherein the probes bind to a multiplicity of upstream and downstream sequences bracketing a multiplicity of regions.

Regarding Claim 8 Bawendi et al teaches a method wherein two oligonucleotide probes are hybridized to a target DNA sequences in close proximity. The two oligonucleotide probes are labeled with two differently colored nanocrystals that can be detected by a microscope (Column 5, lines 40-45 and Fig 3). In the instant case the nanocrystals taught by Bawendi et al are being interpreted as particulate labels because the fluorescent nanocrystals being used are known as Quantum Dots and are particulate and are labels, i.e., they have a diameter of between about 1 nm and about 1000nm (Column 6, lines 14-37). Bawendi specifically teaches that the method of the present invention is useful to determine the proximity of two or more biological compounds to each other and conversely can be used to determine that two or more biological compounds are not in proximity to each other (Column 24 lines 33-40). Bawendi further exemplifies different ways of detecting the fluorescent nanocrystals, one of which uses a microscope (Column 27, lines 50-59). Thus Bawendi et al teach a method of contacting a sample with first and second probes which bracket a region and observing by microscopy the presence or absence of any pairs of the first and second particulate labels as separate points in space.

Regarding Claims 9 and 10 Bawendi teaches that the two oligonucleotide probes are labeled with two differently colored nanocrystals, thus Bawendi teaches that the first and second particulate labels have first and second fluorophores that are distinguishable from each other (Column 5, lines 40-45 and Fig 3). Each nanocrystals is being interpreted as a different fluorophore because each one has different fluorescent properties.

Regarding Claim 11 Bawendi teaches that the nucleic acid probes of the invention are composed any type of polynucleotide including DNA, RNA, and PNA (Column 7 line 26 – Column 8 line 29).

Regarding Claim 12 Bawendi teaches that the first and second probes are complementary to sequences upstream and downstream sequences bracketing the region (Fig 3).

Regarding Claim 13 Bawendi teach a method that when the target is double stranded the first and second probes form triplexes with said upstream and downstream sequences bracketing the region (Column 8, lines 9-12, Fig 3).

Regarding Claim 14 Bawendi discloses a multiplexed method using semiconductor nanocrystals having distinct emission spectra which can be used to detect simultaneously in the range of 2 to 10,000 analytes (Column 11, lines 44-54). Thus Bawendi teaches a method that can be performed simultaneously on a multiplicity of targets using a multiplicity of probes having particulate labels of different hues wherein the probes bind to a multiplicity of upstream and downstream sequences bracketing a multiplicity of regions.

Regarding Claim 15 Bawendi states that the present invention can be used to detect and/or quantitate nucleic acids as follows (a) viral nucleic acids; (b) bacterial nucleic acids; and (c) numerous human sequences of interest (Column 20, lines 23-27). Thus Bawendi teaches a method wherein the target is derived from an organism, wherein the organism is an infectious agent or a human.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

THE FOLLOWING IS A NEW GROUND OF REJECTION:

5. Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bawendi et al (US Patent 6306610 Issued 10/2001) in view of Nie et al (US Patent 6060242).

The teachings of Bawendi are presented above.

While Bawendi teaches that the probe can be a PNA, Bawendi does not teach a method wherein the target nucleic acid is double stranded and the probe forms a triplex with the target nucleic acid.

However Nie et al teach a method which uses a plurality of PNA probes which bind to target nucleic acid sequences. Nie et al further teaches that PNA are able to recognize dsDNA and form triplex complexes with dsDNA (Column 3, lines 20-25).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Bawendi et al by using PNA probes that form triplexes with the target nucleic acid as suggested by Nie in situations where the target nucleic acid being detect is double stranded because PNA probes can recognize dsDNA and hybridize to dsDNA targets.

THE FOLLOWING ARE PREVIOUSLY PRESENTED REJECTIONS:

6. Claims 1-3, 5, 7-10, 12, 14-15, and 17 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Gray et al (US Patent 6475720 Filed 1995) in view of Barbera-Guillem et al (US Patent 6309701 Issued 2001).

Regarding Claims 1-3, 5, 8-10, 12, 14-15, and 17 Gray et al teach a method in which FISH probes from chromosomes 9 (BCR probe) and 22 (ABL probe) were hybridized to metaphase and interphase spreads in order to detect the BCR-ABL fusion in chronic myelogenous leukemia (CML) (Column 58, line 58 to Column 59, line 12 and Fig 11 c-d). The genetic rearrangement of CML brings the DNA sequences homologous to the probes together on an abnormal chromosome. The genomic distance between the probe binding sites in the fusion gene varies among CML cases, ranging from 25 to 225kb (Column 61, lines 4-15). The FISH was carried out using a biotin labeled ABL probe detected with the fluorochrome Texas red, and a digoxigenin

labeled BCR probe detected with the green fluorochrome FITC. Hybridization of both probes could be observed simultaneously using a fluorescent microscope (Column 59, lines 1-12). Therefore Grey teaches a method of using pared probes having first and second labels that hybridize to a target to provide the labels as points separated by space. This separation in space is observed using a fluorescent microscope whereby the presence of the pair identifies the desired region.

Gray et al do not teach that the probes were coupled to particulate labels and that the method can be performed simultaneously on multiple targets using different probes which have different particulate labels of differing hues.

However Barbera-Guillem et al teach a method which utilizes a fluorescent microsphere (comprising fluorescent nanocrystals) coupled to nucleic acid probe to determine the presence or absence of a target nucleic acid in a sample. The target is detected by observing the fluorescence signal pattern of the excited fluorescent microsphere bound to the target using a fluorescent microscope (Abstract, Columns 2, lines 31 to Column 3, line 20). Further Barbera-Guillem et al teach that this method can be used to determine the presence or absence of a single target nucleic acid or multiple target nucleic acids. In the case where multiple targets are present different fluorescent microspheres which emit different colors are used to detect the multiple targets (Example 6).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Gray et al by using a nucleic acid probe coupled to a particulate label (i.e. a fluorescent microsphere

comprising fluorescent nanocrystals) as suggested by Barbera-Guillem. Barbera-Guillem teaches several advantages of using particulate labels (specifically fluorescent microspheres) over conventional fluorescent labels to detect nucleic acid hybridization. The first advantage is that the fluorescent signal produced by fluorescent microspheres is much more intense than the signal produced by conventional fluorescent labels. Additionally fluorescent microspheres have a wider excitation spectrum therefore it is possible to detect multiple fluorescent microspheres which each emit a different hue using a single wavelength spectrum of light. Further fluorescent microspheres are resistant to photo bleaching so there is no limitation on the time in which the fluorescent signal can be detected (Column 1, line 39 to Column 2, line 20). Further the fluorescent microspheres would allow the one to observe the presence or absence of any pairs of the first and second particulate labels as separate points in space.

7. Claims 4, 6, 11, and 13 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Gray et al (US Patent 6475720 Filed 1995) in view of Barbera-Guillem et al (US Patent 6309701 Issued 2001) as applied to claims 1 and 8 above and in further view of Nie et al (US Patent 6060242).

The teachings of Gray et al and Barbera-Guillem et al are presented above.

Regarding Claims 4, 6, 11, and 13 the combined references do not teach a method wherein the first and second probes are peptide nucleic acids. Additionally the combined references do not teach a method wherein the target nucleic acid is double stranded and the probe forms a triplex with the target nucleic acid.

However Nie et al teach a method which uses a plurality of PNA probes which bind to target nucleic acid sequences. Nie et al further teaches that PNA are able to recognize dsDNA and form triplex complexes with dsDNA (Column 3, lines 20-25).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Gray et al by using PNA probes rather than DNA/RNA probes as suggested by Nie in situations where the target nucleic acid being detect is double stranded because PNA probes can recognize dsDNA and hybridize to dsDNA targets.

8. Claim 16 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Gray et al (US Patent 6475720 Filed 1995) in view of Barbera-Guillem et al (US Patent 6309701 Issued 2001) as applied to claims 8 and 15 above and in further view of Ward et al (US Patent 6506563 Filed 1999).

The teachings of Gray et al and Barbera-Guillem et al are presented above.

Regarding Claim 16 the combined references do not teach that the target nucleic acid is derived from an organism wherein the organism is an infectious agent.

However Ward et al teach oligonucleotide probes which are capable of binding chromosomes. The probes taught by Ward are sufficient to permit the characterization of bacteria, viruses and/or lower eukaryotes that may be present in a clinical or non-clinical preparation (Column 2, lines 43-53). In the instant case bacteria and viruses are being interpreted as infectious agents.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Gray et al so as to have used the probes to detect bacterial or viral nucleic acids in order to have achieved the benefits set forth by Ward of providing a method which enables one to asses the presence or absence of infectious agents by employing labeled probes specific for the bacterial or viral sequences.

Response To Arguments

9. In the response filed April 9, 2007, Applicants traversed the rejections made under 35 USC 103. These arguments were addressed in the Advisory Action mailed on April 25, 2007 and will be reiterated below. Further it is noted that the Applicants did not submit any addition arguments after filing the request for continued examination.

Regarding the rejections made under 35 US 103, the Applicants argued that Barbera-Guillem does not teach several advantages of using particulate labels over conventional fluorescent labels to detect "nucleic acid hybridization". Further the Applicants stated that they could not find in the Barbera-Guillem reference that the particlate labels were resistant to photobleaching. This argument has been fully considered and is not found persuasive because Barbera-Guillem teach several advantages of using particulate labels over conventional fluorescent labels (Column 1, lines 37-67) including the resistance to photobleaching (Column 1, line 60). The reference also teaches that the fluorescent microspheres are useful as tagging agents for microarrays, which are considered be nucleic acid hybridization assays. Applicants

further argued that the combination of the Gray and Barbera-Guillem references are not suggested by the art, but by the invention itself, and that no motivation can be found to combined these documents, and that even if combined they fail to suggest the invention as claimed. Applicant's arguments have been fully considered but they are not persuasive. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See In re McLaughlin, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and In re Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). Barbera-Guillem teaches several reasons why one would be motivated to modify the method of Gray. For example Barbera-Guillem teach that fluorescent nanocrystals are resistant to photo bleaching, share an excitation wavelength spectrum, and are capable of emitting fluorescence of high quantum yield with discrete peak emission spectra (Column 1,

lines 58-67). In the instant case Barbera-Guillem is using fluorescent nanocrystal labeled microspheres for fluorescence analysis. Barbera-Guillem et al further teach that these are superior to conventional fluorescent dyes because those dyes typically have a narrow excitation spectrum, it is hard to find a wavelength spectrum of light suitable for simultaneously exciting several different fluorescent labels, and they are susceptible to photo beaching which limits the time in which a signal can be detected (Column 1, lines 58-67). So clearly there are several advantages of using fluorescent nanocrystal labeled microspheres over conventional fluorescent dyes. Therefore one of skill in the art would have been motivated to have modified the method of Gray by using the labels suggested by Barbera-Guillem in order to achieve the benefits of using a fluorescent nanocrystal labeled microsphere rather than a conventional fluorescent dye. Additionally the Applicants argue that the preamble significant in that it imposes limitations on the method steps because the nature of the substrate that would be used in the assay set forth in the body of the claim. The Applicants further state that the substrate used in the instant invention would be different than the substrate used in Gray. First of all it is pointed out that the claims do not recite a particular substrate that is used. In the instant case the claims only require the two probes to bind to a desired region and the Gray reference teaches that. For these reasons the rejections made under 35 US 103 are maintained.

Conclusion

10. No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amanda M. Shaw whose telephone number is (571) 272-8668. The examiner can normally be reached on Mon-Fri 7:30 TO 4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Amanda M. Shaw
Examiner
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PRIMARY EXAMINER